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09/733,756	12/08/2000	David Mack	A-69439/DJB/JJD	2798

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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/733,756

Applicant(s)

MACK ET AL.

Examiner

Jeanine A Goldberg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-35,37-39 and 41-51 is/are pending in the application.
- 4a) Of the above claim(s) 1-6, 8-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32-35,37-39 and 41-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14.
- 4) ☒ Interview Summary (PTO-413) Paper No(s). 15.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 2, 2002.
2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
3. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments, and the amendments to the claims.
4. Claims 32-35, 37-39, 41-51 have been examined on the merits.
5. Claims 1-6, 8-30 have been withdrawn from consideration as drawn to non-elected claims.

Maintained Rejections

Drawings

6. The drawings are objected by the examiner.

Figures 1 and 2 contain sequences. The sequences are neither identified by SEQ ID NO: on the figure or in the figure legend.

Figure 3A-D have holes in the vertical axis. Increasing the top margin of the page would eliminate the holes in the axis.

Response to Arguments

The response asserts that substitute sheets of Figure 1 and 2 have been submitted. The figures have not been received in the instant application. Further, the transmittal sheet does not appear to indicate that they were provided. Moreover, the objections to Figures 3A-D have not been addressed.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 32-35, 37-39, 41-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for diagnosing breast cancer or colorectal cancer by determining the expression level of a gene which is at least 95% identical to SEQ ID NO: 1.

The specification teaches that SEQ ID NO: 1 corresponds to the gene CHA4. CHA4 nucleic acid and amino acid sequences are shown in Figure 1 and 2, respectively. Figures 3A illustrates the relative amount of expression of CHA4 in

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various samples of breast cancer tissue; Figure 3B illustrates colorectal cancer tissue; and Figures 3C-3D illustrate several normal tissue types. With respect to Figure 3A directed to breast cancer tissue, the expression level in the tissues appears to range from 100-750 (no units provided). Turning to Figure 3C, normal breast tissue appears to range from 80-400 (no units provided). As seen in Figure 3A, 54 of the samples had expression within the "normal" range of expression. 54 of the 66 (83%) breast cancer tissues had expression levels less than 400. Therefore, there does not appear to be differential expression between the breast cancer tissues of Figure 3A and the 7 breast normal tissues of Figure 3C.

With respect to Figure 3B directed to colorectal cancer tissue, the expression level in the numerous tissues appears to range from 100-740 (no units provided). Turning to Figure 3C, normal colon appears to range from 100-200. 11 of the 78 (14%) colorectal tissues had expression levels less than 200. Therefore, the ranges of normal and cancerous expression levels of CHA4 overlap.

The art teaches what is called CHA4 in the specification has also been referred to as Ephrin-A3, EphA3, hek-L, Lerk-3, ehk1-L, and Ehk1. Beckmann et al. (US Pat. 5,516,658, May 1996) teaches Hek ligand (hek-L) polypeptides and nucleic acids encoding the polypeptides. The Hek-L polypeptides, SEQ ID NO: 2 of Beckmann and SEQ ID NO: 2 of the instant application are 100% identical over all 238 amino acids. The nucleic acid of Beckmann, namely SEQ ID NO: 1 and the instant SEQ ID NO: 1 share 52.7% identity over the full length with a best local similarity of 99.8% (see attached alignment). Beckmann teaches a human T-cell leukemia cell line expresses

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the Hek-L nucleic acid. Beckmann does not specifically teach using the Hek-L for diagnostic of cancers.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. The specification and claims of the instant application assert that detection of the expression of a gene comprising at least 95% identity with SEQ ID NO: 1 allows for diagnosis of colorectal cancer. The evidence for this assertion provided in the specification, in Figure 3A-3D, Example 3, page 68, does not appear to support the assertion. As provided in the analysis above, the ranges for "normal" and "cancerous" tissue expression of CHA4 overlap in both breast and colon cancers analyzed. There is no indication in the specification of a threshold which would be indicative of colon or breast cancer tissue. Therefore, distinguishing a cancerous tissue from a normal tissue based solely on different sample expression would be unpredictable. While one could conduct additional experimentation to determine whether, e.g., expression of SEQ ID NO: 1 at certain levels might be associated with, e.g., certain types of colorectal or breast cancers, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

Furthermore, the teachings of the prior art do not provide evidence of how to use the methods in which expression of SEQ ID NO: 1 or genes which are at least 95% identical with SEQ ID NO: 1 are an indicator of breast or colorectal cancer. The specification does not teach any analysis of variants of SEQ ID NO: 1 which are 95% identical with SEQ ID NO: 1. These variants may include variants which afford a

protective effect to the nucleic acid such that they are indicative of lower risk for cancer. The variants also include splice-variants, SNPs, mutations, deletions, insertions which may have different diagnostic implications on the nucleic acids. Without undue and unpredictable experimentation, the skilled artisan would not be aware of which of the variants would have which effects on the risk of breast or colon cancers.

With respect to Claims 44-47, the specification does not teach how expression of SEQ ID NO: 1 or nucleic acids 95% identical with SEQ ID NO: 1 are predictive of prognosis. The specification does not teach any levels of expression which provide extremely poor prognosis, as opposed to which levels of expression are deemed to be indicative of good prognosis. There are not thresholds or ranges which delineate any prognosis levels for individuals.

The teachings of the specification do not establish that one could actually detect expression of SEQ ID NO: 1 or genes which are at least 95% identical with SEQ ID NO: 1 as an indicator of colorectal or breast cancer. Rather the teachings of the specification assert that SEQ ID NO: 1 is expressed at higher levels in the colon and breast tissue than in other human tissue types, as discussed above. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, namely Beckmann, does not provide support for the use of SEQ ID NO: 1 expression as an indicator of colorectal or breast cancer. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between

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SEQ ID NO: 1 or variants of 95% identity with SEQ ID NO: 1 expression and colorectal or breast cancer, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Response to Arguments

The response traverses the rejection. The response attempts to support their assertions with respect to the ability of gene expression analysis as a means to diagnosis/prognosis of cancer by submitting "The National Cancer Institute Fact Sheet 5.18." It is noted that the examiner, on December 23, 2002, December 31, 2002 attempted to obtain a copy of this fact sheet from applicants. In response to the examiner's request, the applicant submitted an IDS containing three foreign patent documents. Therefore, the examiner does not have a copy of the fact sheet to analyze nor review. Moreover, the information provided to the examiner is not sufficient to seek the fact sheet elsewhere, as there is no information with respect to date, author or publisher. However, in an effort to expedite prosecution, applicant's arguments are addressed to the extent possible without the document.

The response asserts "despite the presence of markers in normal tissue, the fact sheet states that detection of tumor/cancer makers provides a useful tool for the detection and diagnosis of some types of cancer when used along with x-rays or other tests" (page 9, para 3 of response filed December 2, 2002). This argument has been reviewed but is not convincing because the instant specification does not provide any indication of how one would detect a tumor/cancer using the information provided in the

specification. It is noted that the asserted novelty of the invention lies in the asserted overexpression of SEQ ID NO: 1 in cancers. The claims are broadly drawn to methods of comparing expression of nucleic acids in two samples to evaluate overexpression as a diagnostic of cancer. Therefore, the specification must enable the skilled artisan to diagnose cancer using overexpression. As previously provided, the specification teaches the overlapping ranges of normal and cancer expression of SEQ ID NO: 1, therefore, the skilled artisan would be required to perform additional experimentation to practice the invention as claimed.

The response points to examples of genes which have been highly studied, such as PSA, PAP, CA125, CEA, AFP etc, which are overexpressed in cancer. The response asserts that PSA is elevated in men with a malignant growth in the prostate, but may also be elevated in the blood of men with benign prostate conditions. The response states that "in checking PSA levels, doctors generally look for trends, such as steadily increasing PSA levels in multiple tests over time, rather than focusing on a single elevated result" (page 9, para 4 of the response filed December 2, 2002). This argument has been thoroughly reviewed, but is not found persuasive because the specification has stated that PSA is examined over time with trends rather than "focusing on a single elevated result" which appears to be precisely what was studied in the instant specification. Therefore, the information regarding PSA is not analogous to the information provided in the instant specification.

The response provides that PAP is found at higher levels in some patient with prostate cancer, especially if the cancer has spread beyond the prostate. This gene is

not analogous to the instant situation since, the ranges of normal do not overlap diseased. Similarly, CA125 is overexpressed in individuals with cancer and other conditions.

Based upon the assertions by the response and the knowledge in the art at the time the invention was made, the examiner acknowledges that some genes, once characterized, have diagnostic value in evaluating cancer and other conditions. However, the instant specification does not provide the skilled artisan with enough guidance to use the invention as claimed.

The response asserts that the specification has shown that certain cancers can be identified by examining the expression patterns of SEQ ID NO: 1. The response states that "at least 17% of breast cancers have expression levels of CHA4 that are higher than the highest levels of expression seen in normal tissue" (page 11, para 1 of the response filed December 2, 2002). This argument has been thoroughly reviewed, but is not found persuasive because the skilled artisan would be unable to make an accurate "diagnosis" based upon the overexpresion of 17% of the breast cancers. Moreover, CHA4 is not overexpressed in all of the cancers.

The response asserts that based upon a teaching in the art that "tumor marker levels are not elevated in every person with cancer, especially in early states of the disease" (page 11, para 2 of the response filed December 2, 2002). Moreover, the response asserts that "applicants have provided data showing that increased levels of CHA4 expression are correlated in a statistically significant manner with breast and/or colorectal cancer" (page 11, para 3, response filed December 2, 2002). This argument

has been thoroughly reviewed, but is not found persuasive because the examiner has not found any statistical analysis performed by the instant specification. The examiner does not believe that the presence of an overexpression in 17% of the breast cancers is a significant result.

The response suggests that "detection of CHA4 expression at a level indicative of breast or colorectal cancer will suggest that further tests be conducted to confirm the diagnosis of breast or colorectal cancer." This argument has been thoroughly considered, but is not found persuasive because the specification has failed to provide any "threshold" or "level" which the skilled artisan would recognize as cancerous. The skilled artisan would be required to perform additional experimentation to determine the appropriate thresholds of CHA4 expression to practice the invention as claimed.

The response asserts that "since increased expression is associated with cancer, it follows that higher levels of expression will correlate with a poorer prognosis evaluation for the patient" (page 12, para 1, response filed December 2, 2002). This correlation has not been established in either the specification nor the art. As discussed above, it is unclear whether SEQ ID NO: 1 is associated with cancer based upon the lack of statistical evidence. Further, the specification is completely silent with respect to poorer prognosis based upon the increased expression of CHA4. The evidence of record, namely Figures 3A-3D demonstrate that given a test sample from a patient and a control sample, it is unpredictable that detection of overexpression would be indicative of cancer since many of the cancer and normal cells are within the same range and are undistinguishable.

With respect to the specification being enabling for sequence variants comprising SEQ ID NO: 1, the response asserts that the claim encompasses variations as would be expected to occur naturally within the entire human population. This argument has been thoroughly reviewed, but is not found persuasive because mutations within the coding sequence of the gene likely change the amino acid sequence such that the protein encoded differs in structure and often times in function. Therefore, it is unpredictable whether all of the variants encompassed by the claims are expressed in the same manner as SEQ ID NO: 1. Absent undue, unpredictable experimentation, the skilled artisan would be required to perform additional experimentation to determine whether the expression levels of any variant is associated with cancer by overexpression.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 32-35, 37-39, 41-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 32-35, 37-39, 41-43, 48-51 are indefinite over the recitation
“comparing the expression of said nucleic acid in the first sample to expression of said

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nucleic acid in a second sample; wherein an increase in expression of said nucleic acid in the first sample relative to the second sample provides a diagnosis of breast cancer or colorectal cancer in the first individual." This recitation does not specifically set forth the origin of the second sample. The second sample could be either normal or cancerous tissue. It is unclear whether the second sample is either disease or normal. The specification does not appear to support a method wherein the second sample is diseased since the specification does not support an increase expression over a cancerous sample as indicative of cancer.

B1) Claims 44-47 are indefinite over the recitation "high level of expression of said sequence indicates a poor prognosis from an individual." The term "high level of expression" in claim 44 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Since neither the specification nor the art teaches the level of expression necessary to indicate a poor prognosis, the claim does not provide adequate metes and bounds for the claimed invention. Thus, the metes and bounds of the claimed invention are indefinite.

Conclusion

9. **No claims allowable.**

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
February 11, 2003

Gary Benzion
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